Explor Anim Med Res,
Vol.10, Issue - 2, 2020, p. 97-99

ISSN 2277- 470X (Print), ISSN 2319-247X (Online)
Website: www.animalmedicalresearch.org

*Editorial*

# DIETARY MODULATION WITH FATTY ACIDS: A POTENTIAL WAY TO OVERCOME COVID-19

Novel coronavirus (SARS-CoV-2) infection or the so called COVID-19 has created a global crisis killing lakhs of people so far and crippling every sphere of human activity such as economy, education, social life, etc. The virus is extremely infectious and causes illness with diverse signs and symptoms affecting several body parts, notably brain, lungs, digestive system, cardio-vascular system, kidney, etc. Very few viral infections have such a wide spectrum of tissue tropism and clinical signs, despite its low fatality rate of only about 2.7% (WHO 2020). A key feature is the relatively high morbidity and mortality among the greying and aged population.Type 2 diabetes, hypertension, cardiovascular diseases which are now frequently common among global populations are major comorbidities of the disease. Another cause of concern is the prolong recovery period - COVID-19 survivors may suffer from extreme weakness and sudden collapse, impaired/reduced cognition, lack of energy, etc. for very long period extending for months or even more.

The virus uses the ACE2 receptor protein for attachment and cell entry which is widely distributed throughout the body and found in high levels in lungs, kidney etc. making these organs highly prone to virus-induced changes and failure. A sudden onset of cytokine storm and intravascular micro-coagulations in vital organs are the immediate causes of death in COVID-9. Intensive researches across the globe are now unrevealing metabolic modulations of host cells as the primary mechanism of the virus pathogenesis. SARS-CoV-2, unlike some other common human viruses such as influenza A ($H_1N_1$) virus and respiratory syncytial virus, cause widespread metabolic reprogramming for its own benefits which is possibly the cause of diverse clinical signs and prolonged recovery period (Ehrlich *et al*. 2020). Plasma metabolomic study also indicated altered carbohydrate, protein and lipid metabolism, and in particular decreased levels of malic acid, D-xylulose 5-phosphate and carbamoyl phosphate in COVID-19 patients (Wu *et al.* 2020).

## SARS-CoV-2 disrupts glucose oxidation

Among several clinic-pathological changes, dysregulated sugar metabolism, expressed as persistent hyperglycaemia, and onset of diabetes among non-diabetics suggest that glucose metabolism is highly perturbed (Codo *et al.* 2020). Hyperglycaemia has been linked to over-secretion of proinflammatory cytokine IL-6 leading to cytokine burst and multiple organ failure. *In vitro* experiment also showed that high glucose level increases the viral load and expressions of ACE2, IL-1β, IL-6, TNF-α, and IFN α, β, and λ in CoV-2-infected monocytes in a concentration-dependent manner favouring the viral infection and outcome. The virus also promotes T cell dysfunction and pulmonary dysfunction encountered in severe COVID-19 cases (Codo *et al*. 2020).

The virus causes mitochondrial elongations, altered TCA cycle, glycolysis and pentose phosphate pathways, besides alteration of protein and lipid metabolism, favouring nucleotide and lipid synthesis for virus replication. However, among the whole plethora of metabolic alterations, dysregulation of sugar metabolism, especially glycolysis is the most prominent. Metabolomic study of lung tissue also shows uncoupling of TCA cycle and oxidative phosphorylation, and upregulation of anaerobic glycolysis: the virus upregulates glycolysis and hijacks the energy pathways for its replication (Ehrlich *et al.* 2020). Uncoupling of cellular respiration cause oxidative stress which is again linked to severity of the infection. The over-activated glycolysis may also be correlated with many folds increase in serum lactate dehydrogenase enzyme (LDH) levels in severely affected and terminal patients (Henry *et al.* 2020). SARS-CoV-2 inhibits the pyruvate dehydrogenase complex forcing body into energy crisis and cytokine burst.

Glucose is the major energy source of body, especially in brain, lungs, kidney, etc. and altered glycolysis and energy generation pathways affect functioning of these organs. Since glucose enters metabolism/energy generation pathways through glycolysis altered dehydrogenases and diverting glycolysis for synthesis of virus molecule and thus depriving body of energy is likely to affect body for long term. This is a likely reason of extreme weakness and long recovery period among the

COVID-19 survivors. Further, glucose oxidation by body decreases with age. The low level of glycolysis activity might predispose one to severe COVID-19 infection in old age.

**Fatty acids as a saviour**

Since the virus inhibits dehydrogenases and hijacks glycolysis-driven energy pathway, carbohydrate-based diet is supposed to enhance the disease severity. Unlike glucose, fatty acids and amino acids do not enter the TCA cycle through glycolysis. Further, level of glucose utilization in elderly and diabetic individuals are low. Hence enhancing cell metabolism other than of sugars may control virus growth and provide energy to the cells for survival and mounting of interferon and other innate immune responses at the cell level. Although transcriptomic and metabolomic studies show that the virus also alters lipid metabolism, there are inconsistent observations on the effect of virus on lipid metabolism. Unlike enhanced blood glucose levels, concentrations of blood lipids decrease with severity of the infection and are inversely correlated with IL-6 levels (Wei *et al.* 2020). Metabolomic study indicated that the virus alters lipid metabolism with higher levels of triglycerides and cholesterol in COVID-19 patients. Since cholesterol is essential for virus synthesis and release, use of cholesterol synthesis inhibitors such as statins has been suggested against the virus (Abu-Farha *et al.* 2020).

From published literatures it seems that aberration in lipid and protein metabolism is low as compared to the sugar metabolism in COVID-19. When glycolysis is unable to provide energy in COVID-19, it is essential that body must oxidise fat and proteins for energy generation. Drugs like fenofibrate and oleoylethanolamide which stimulate fatty acid oxidation have also been proposed as a promising treatment of the disease (Ghaffari *et al*. 2020). High-fat diet and/or exogenous ketone supplementation have been suggested to provide energy essential for every cell and prevent cytokine burst (Bradshaw *et al.* 2020). Further, omega-3 fatty acids are known to have anti-inflammatory properties and thus foods rich in these PUFA might provide energy as well as protection against inflammatory reactions (Calder 2020). However, the virus triggers lipogenesis for envelop synthesis and use of more fat during active stage of the infection might enhance the disease severity (El-Kurdi and Khatua 2020). Thus, instead of using fat during acute stage, fatty foods might prime body to oxidize fat for energy during healthy state and may favour faster recovery as well.

Besides above functions, binding of unsaturated fatty acids such as linoleic acid, etc. to surface spike glycoproteins of enveloped viruses including SARS-CoV-2 destabilizes their structural integrity and reduces virus interactions with ACE2 receptor proteins leading to reduced virus infection (Toelzer *et al.* 2020). Dietary fatty acids have also been suggested as a possible way to reduce inflammatory changes in lungs, intestine, etc. in COVID-19 conditions (Calder 2020, Onishi *et al.* 2020).

It is expected that taking enough fat and protein rich food might save a life and enhance recovery. Hence nutritious foods rich in minerals, vitamins and especially those rich in unsaturated fatty acids have been suggested to prevent the COVID-19 (Calder 2020, Onishi *et al.* 2020). The global population will have to live with the virus for long till vaccines are made available to the huge susceptible population. Till then let the fatty foods rich in MUFA and omega-3 rich fatty acids such as fish, the potent vegetable oils, nuts, fruits, and milk be our weapons to fight against the virus.

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**Cite this article as:** Mandal TK, Pattanayak S (2020) Dietary modulation with fatty acids: a potential way to overcome COVID-19. Explor Anim Med Res 10(2): 97-99.